JACC

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Contents

CARDIOLOGISTS

Scott & White and the Texas A&M University College of Medicine, Temple, Texas, are recruiting for an additional BE/BC Cardiologist with an interest in both non-invasive and general cardiology to join our ten member Division of Cardiology. The candidate should have a strong interest in teaching with proven success in patient management and fully qualified to perform all echo/doppler studies to include transesophageal echo (TEE).

Located in Central Texas, Scott & White physicians have access to year around recreational facilities. Austin, Dallas and San Antonio are only a few easy miles away.

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CARDIOLOGY

Nine member Cardiology group practice in southeast university city seeks BE/BC Cardiologists for the following positions:

A. Electrophysiologist to direct full-service EP program in dedicated lab.
B. Clinical Cardiologist with special interest in lipid management and/or cardiac rehabilitation.
C. Clinical Cardiologist with interest in a non-interventional practice (duties may include diagnostic catheterization).
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All positions offer competitive salary, early partnership, and excellent benefits package.

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NON-INVASIVE CARDIOLOGIST

BE/BC non-invasive cardiologist to join a 5 physician invasive & non-invasive cardiology practice. We are involved in all aspects of adult cardiology & are located 20 minutes north of Boston, MA. This position is available 7/1/93.

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CARDIOLOGISTS

Two Cardiologists are needed to join Carle Clinic Association, one invasive with angioplasty experience and one non-invasive to join seven cardiologists. Full array of cardiology services and established surgical program. Academic positions available at the University of Illinois. Benefits include competitive salary with partnership and income sharing plan after two years; professional liability, health, life and disability insurance, and generous vacation and meeting time.

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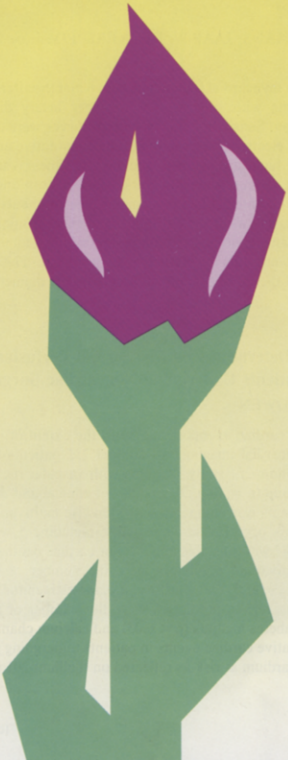
A Cardiovascular Drug



New from

SCHWARZ
PHARMA

SP1164 1/93

The relations among intracoronary ultrasound, angiographic and histologic morphometric characteristics were analyzed in 52 patients (mean age 54 years) successfully treated by directional coronary atherectomy. In 22 of these patients, follow-up ultrasound-angiographic reevaluation was performed. Echogenic plaques had a higher collagen and calcium content, whereas echolucent plaques had an increased level of fibrin, cells and lipids. Ultrasound plaque reduction after atherectomy was more complete in echolucent than in echogenic plaques. However, the resection of dense echogenic plaques, although frequently incomplete, was associated with better long-term results.

308 Analysis of Coronary Blood Flow Velocity Dynamics in Angiographically Normal and Stenosed Arteries Before and After Endolumen Enlargement by Angioplasty

ELIZABETH O. OFILI, MORTON J. KERN, ARTHUR J. LABOVITZ, JEANETTE A. ST. VRAIN, JEROME SEGAL, FRANK V. AGUIRRE, RAMON CASTELLO

Coronary flow velocities were obtained with a 12-MHz 0.018-in. (0.46 cm) spectral Doppler guide wire in 17 normal and 29 significantly stenosed coronary arteries. Measurements were obtained at baseline and after pharmacologically induced hyperemia. Spectral Doppler mean velocity and vasodilator reserve correlated with previously validated zero cross catheter measurements in normal arteries ($r = 0.89$ and 0.93, respectively). Spectral Doppler velocity variables were significantly higher in normal than in stenosed arteries. Blunting of coronary flow velocity variables in abnormal arteries was more marked distal to the stenosis; successful angioplasty resulted in marked increases in distal velocities with near equalization to proximal velocities resulting in a significant reduction in the proximal distal flow velocity ratio (2.4 ± 1.7 before vs. 1.2 ± 0.2 after angioplasty, $p < 0.02$). Thus, near normalization of distal velocities with marked reduction in proximal/distal flow velocity ratio may prove useful in evaluating the results of revascularization.

317 Which Angiographic Variable Best Describes Functional Status 6 Months After Successful Single-Vessel Coronary Balloon Angioplasty?

BENNO J. RENSING, WALTER R. M. HERMANS, JAAP W. DECKERS, PIM J. DE FEYTER, PATRICK W. SERRUYS

To determine angiographic cutoff points at which myocardial ischemia occurs 6 months after a coronary angioplasty procedure, we studied 350 patients with single-vessel coronary artery disease who underwent a successful single-site balloon dilation. Sensitivity and specificity curves were constructed for the prediction of anginal status and exercise electrocardiography of four quantitative angiographic variables 6 months after dilation. The point of highest diagnostic accuracy for these variables was determined at the point of intersection of these curves. Values were similar for both anginal status and exercise electrocardiography: 1.45 mm for the minimal lumen diameter measurements, 45.5% for the percent diameter stenosis measurements at follow-up, −0.30 mm for change in minimal lumen diameter and −10% for the change in percent diameter stenosis at follow-up. Minimal lumen diameter and percent diameter stenosis measurements were equally predictive of ischemia. The unambiguous minimal lumen diameter measurement can therefore reliably replace percent diameter stenosis measurements in restenosis prevention trials.

Myocardial Ischemia

325 Extent of Jeopardized Viable Myocardium Determined by Myocardial Perfusion Imaging Best Predicts Perioperative Cardiac Events in Patients Undergoing Noncardiac Surgery

KENNETH A. BROWN, MICHAELANNE ROWEN

To determine whether the perioperative risk of cardiac events is related to the extent of jeopardized viable myocardium based on thallium-201 myocardial imaging, we studied 231 patients undergoing noncardiac surgery who had a preoperative thallium-201 study. Patients with vascular reconstruction or bypass constituted the largest surgical subgroup ($n = 140$). The ability of clinical and thallium-201 imaging data to predict perioperative cardiac events was compared with stepwise multivariate logistic regression analysis. Perioperative cardiac events occurred in 19 patients, including 5 with cardiac death, 7 with nonfatal myocardial infarction and 7 with unstable angina. For cardiac death or nonfatal myocardial infarction, the only significant multivariate predictors were the number of myocardial segments with transient thallium-201 defects ($p < 0.0005$) and a history of diabetes mellitus ($p < 0.05$). For all cardiac events, the only significant multivariate predictors were the number of myocardial segments with transient defects ($p < 0.0001$), diabetes mellitus ($p < 0.05$) and calcium channel blocker use ($p < 0.05$). Thus, the probability of perioperative cardiac events in patients undergoing noncardiac surgery is directly related to the extent of myocardium at risk as reflected on thallium-201 myocardial perfusion imaging.

TWO LANDMARK STUDIES,[1,2]
PRESENTED AT THE
1992 AMERICAN COLLEGE OF
CARDIOLOGY MEETING,

FINALLY RESOLVED

LANOXIN IS EFFECTIVE IN CONGESTIVE HEART FAILURE PATIENTS IN NORMAL SINUS RHYTHM, WITH OR WITHOUT AN ACE INHIBITOR.[1,2*†]

*The RADIANCE—Randomized Assessment of Digoxin on Inhibitors of the ANgiotensin Converting Enzyme—study was a multicenter, randomized, double-blind, placebo-controlled study of digoxin in CHF patients receiving diuretics *and* ACE inhibitors.

†The PROVED—Prospective Randomized study of Ventricular failure and the Efficacy of Digoxin—study was a multicenter, randomized, double-blind, placebo-controlled study of digoxin in CHF patients receiving diuretics.

In early CHF.

LANOXIN®

(digoxin) Tablets 125 µg (0.125 mg) 250 µg (0.25 mg) 500 µg (0.5 mg)

EFFECTIVE THERAPY... WITH OR WITHOUT AN ACE INHIBITOR.

Please see brief summary of prescribing information below.

LANOXIN® (DIGOXIN) TABLETS

Before prescribing, physicians should be thoroughly familiar with all aspects of this cardiac (or digitalis) glycoside as discussed in the full prescribing information.

Brief Summary

CONTRAINDICATIONS:
(1) ventricular fibrillation, (2) an untoward effect requiring discontinuation of other digitalis preparations, and (3) a hypersensitivity or allergy to digoxin.

WARNINGS: The use of digoxin for the treatment of obesity is dangerous since it may cause potentially fatal arrhythmias. Anorexia, nausea, vomiting and arrhythmias may be indications of digitalis toxicity; if so, digoxin should be temporarily withheld when possible. Patients with renal insufficiency require smaller than usual maintenance doses of digoxin. Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization and careful monitoring. Relatively low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary. Digoxin should be discontinued as soon as possible in this setting. Patients with severe carditis are especially sensitive to digoxin-induced rhythm disturbances. Newborn infants display considerable variability in their tolerance to digoxin with premature and immature infants being particularly sensitive; reduce and individualize dosage accordingly. Note: Digoxin is an important cause of accidental poisoning in children.

PRECAUTIONS: Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Normal potassium and magnesium levels should be maintained in patients treated with digoxin. Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypercalcemia predisposes the patient to digitalis toxicity, whereas hypocalcemia can cause digoxin to become ineffective. Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced rhythm disturbances. Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias; if large doses are required, be careful to avoid toxicity. In hypothyroidism, digoxin requirements are reduced. Reduction of digoxin dosage may be desirable before electrical cardioversion to avoid induction of ventricular arrhythmias. If digitalis toxicity is suspected, elective cardioversion should be delayed. Patients with incomplete AV blocks may progress to advanced or complete heart block when given digoxin, especially in patients with Stokes-Adams attacks. Digoxin may worsen sinus bradycardia or sinoatrial block in patients with sinus node disease. Digoxin may cause rapid ventricular rates and ventricular fibrillation in patients with Wolff-Parkinson-White Syndrome and atrial fibrillation. Because it may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS), digoxin should only be used in severe cardiac failure in this setting. Patients with chronic constrictive pericarditis may fail to respond to digoxin. Slowing of the heart rate by digoxin in some patients may further decrease cardiac output. Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to digoxin. (See DRUG INTERACTIONS section.)

Laboratory Tests: Serum electrolytes and renal function should be assessed periodically.

Drug Interactions: Potassium-depleting *corticosteroids* and *diuretics* may be major contributing factors to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. *Quinidine, verapamil, amiodarone,* and *propafenone* cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. Certain *antibiotics* increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. *Propantheline* and *diphenoxylate,* by decreasing gut motility, may increase digoxin absorption. *Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine,* certain *anticancer drugs* and *metoclopramide* may reduce intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. There have been inconsistent reports regarding the effects of other drugs on the serum digoxin concentration. *Thyroid* administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias because both enhance ectopic pacemaker activity. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although ß adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

Carcinogenesis: No long-term animal studies have been performed to evaluate carcinogenic potential.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with digoxin. Digoxin should only be given to a pregnant woman if clearly needed.

Nursing Mothers: Studies have shown that the digoxin concentration in the mother's milk is far below the usual infant maintenance dose and should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

ADVERSE REACTIONS: The overall incidence of adverse reactions has been reported as 5 to 20%, with 15 to 20% (1 to 4% of all patients) of them being considered serious. Evidence suggests that the incidence of toxicity has decreased since the introduction of the serum digoxin assay and improved standardization of digoxin tablets. Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.

Adults: ***Cardiac***–unifocal or multiform VPCs; ventricular tachycardia, AV dissociation, accelerated junctional (nodal) rhythm and atrial tachycardia with block; excessive slowing of the pulse, AV block (Wenckebach) of increasing degree may proceed to complete heart block.

Gastrointestinal: anorexia, nausea, vomiting, occasionally diarrhea, and very rarely hemorrhagic necrosis of the intestines and abdominal pain.

CNS: visual disturbances, headache, weakness, dizziness, apathy and psychosis.

Other: gynecomastia.

Infants and Children: Anorexia, nausea, vomiting, diarrhea and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. Most common are conduction disturbances or SVTs, such as atrial tachycardia with or without block, and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin toxicity, especially in infants, even in the absence of first degree heart block.

September 1991 542253

PLEASE CONSULT FULL PRODUCT INFORMATION BEFORE PRESCRIBING

References: 1. Packer M, Gheorghiade M, Young JB, et al. Randomized, double-blind, placebo-controlled, withdrawal study of digoxin in patients with chronic heart failure treated with converting-enzyme inhibitors. *J Am Coll Cardiol.* 1992;19:260A. Abstract. **2.** Young JB, Uretsky BF, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Multicenter, double-blind, placebo-controlled randomized withdrawal trial of the efficacy and safety of digoxin in patients with mild to moderate chronic heart failure not treated with converting enzyme inhibitors. *J Am Coll Cardiol.* 1992;19:259A. Abstract.

Wellcome **Burroughs Wellcome Co.**
Research Triangle Park, NC 27709

(continued on page A-35)

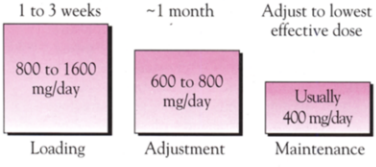
Treatment of patients with serious, life-threatening ventricular arrhythmias is one of the most challenging tasks facing cardiologists today, especially so in the post-CAST era. Fortunately, there's Cordarone® (amiodarone HCl), a Class III agent that extends the treatment options available to physicians. Used at the lowest effective dose, Cordarone can help you achieve and maintain therapeutic success and reduce side effects.

Fortunately,

Minimum effective dose, maximum patient benefit

Following a loading dose and an adjustment period, the dosage should be decreased to the lowest amount consistent with adequate therapeutic results. Many patients can be well managed with approximately 400 mg of Cordarone per day. Using the lowest effective dosage helps reduce adverse reactions. In all instances, dosage must be guided by the severity of the arrhythmia and the patient's response to treatment.

Guidelines for dose reduction



Highly effective in preventing recurrence

Clinical studies with follow-up periods ranging from 10.3 to 26 months have shown that low-dose Cordarone prevents the recurrence of arrhythmias in 78 to 85 percent of patients with life-threatening ventricular tachycardia or ventricular fibrillation.[1,2] In most cases, recurrence rates in patients who were judged to have responded well enough to be placed on long-term treatment have ranged from 20 to 40 percent in series with a mean follow-up of a year or more.[3]

As is the case for other antiarrhythmic agents, there is no evidence from controlled trials that the use of Cordarone favorably affects survival.

Periodic monitoring to maintain benefit

Monitoring of effectiveness and safety is an important element of managing patients on Cordarone therapy because its use has been associated with adverse effects, some of which are serious. Side effects have occurred in about three fourths of all patients and have caused discontinuation in 7 to 18 percent. Several series studied have reported as high as 20 percent discontinuation. Withdrawal rates due to adverse effects in patients taking Cordarone are comparable to those with Class I agents.[4]

Serious adverse reactions associated with Cordarone use include pulmonary toxicity (2-7% in most studies but as high as 10-17% in some reports, with fatalities in about 10% of cases),* liver-function test abnormalities (4-9%), hyperthyroidism (about 2%) and hypothyroidism (2-4% in most series, but as high as 8-10% in some series) and proarrhythmia (2-5%).

Less serious but more common side effects that rarely require drug discontinuation include neurologic effects (20-40%), including malaise and fatigue, tremor and involuntary movements, poor coordination and gait, and peripheral neuropathy; gastrointestinal complaints (about 25%), most commonly nausea, vomiting, constipation and anorexia; asymptomatic corneal microdeposits in virtually all adults who have been on the drug for over 6 months; and dermatologic effects in about 15% of patients, the most common being photosensitivity, which has been reported in about 10%.

* Data suggest that the use of lower loading and maintenance doses of Cordarone is associated with a decreased incidence of Cordarone-induced pulmonary toxicity. Other factors associated with but not having a direct causative effect on the incidence of Cordarone-induced pulmonary toxicity include advanced age, lower pretreatment pulmonary DLCO and higher plasma desethylamiodarone concentrations.

See adjacent page for brief summary of prescribing information.

Suggested follow-up protocol for patients receiving Cordarone®

Follow-up Assessment	Baseline	3 mos.	6 mos.	12 mos.	With Symptoms
ECG	X	X	X	X	X
Pulmonary function	X				X
Chest X-ray	X	Every 3-6 months			X
Thyroid	X		X	X	X
Liver enzymes	X		X	X	X
Serum lipids	X		X	X	As indicated

Adapted from B.N. Singh. How to follow a patient on chronic amiodarone therapy. Choices Cardiol 1989;3(suppl 3):16-20.

Shaded areas reflect additional recommendations from product labeling.

References:

1. Greenberg ML, Lerman BB, Shipe JR, et al. Relation between amiodarone and desethylamiodarone plasma concentrations and electrophysiologic effects, efficacy and toxicity. *J Am Coll Cardiol* 1987;9:1148-1155.
2. Haffajee CI, Love JC, Alpert JS, et al. Efficacy and safety of long-term amiodarone in treatment of cardiac arrhythmias: dosage experience. Am Heart J 1983;106:935-943.
3. Cordarone® prescribing information.
4. Nygaard TW, Sellers TD, Cook TS, et al. Adverse reactions to antiarrhythmic drugs during therapy for ventricular arrhythmias. JAMA 1986;256:55-57.

there's Cordarone®

For patients with recurrent VT/VF refractory to or intolerant of other agents

Cordarone®
(amiodarone HCl)
200 mg tablets

Helping you meet the challenge

WYETH-AYERST LABORATORIES
Philadelphia, PA 19101

Cordarone® (amiodarone HCl) Tablets

BRIEF SUMMARY.
(See Package Circular for full prescribing information.)

Indications and Usage: Because of life-threatening side effects and substantial management difficulties (See "Warnings" below) use only for treating documented, life-threatening recurrent ventricular fibrillation or recurrent hemodynamically unstable ventricular tachycardia that are unresponsive to documented adequate doses of other antiarrhythmics or when alternative agents are not tolerated.

Comorbid risks should not be considered when choosing Cordarone for a life-threatening arrhythmia.

For use only by physicians familiar with and with access to (directly or via referral) all available medical care for treating recurrent life-threatening ventricular arrhythmias, including access to appropriate monitoring facilities and continuous electrocardiographic monitoring and electrophysiologic techniques. Due to the life-threatening nature of the arrhythmias treated, potential interactions with prior therapy, and potential for adverse effects, patients should be hospitalized during initiation of therapy and any dosage adjustment.

Contraindications: Severe sinus node dysfunction, with associated sinus bradycardia. 2nd- and 3rd-degree atrioventricular (AV) block, episodes of bradycardia which cause syncope (except when used with a pacemaker), known hypersensitivity to the drug.

Warnings: Cordarone is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.

Cordarone has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10 to 17% in some series of patients with ventricular arrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal about 10% of the time. Liver injury is common with Cordarone, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. Like other antiarrhythmics, Cordarone can exacerbate the arrhythmia, e.g., by making the arrhythmia less well tolerated or more difficult to reverse. This has occurred in 2% of patients in various series, and significant heart block or sinus bradycardia has been seen in 4-5%. Adverse events should be manageable in the proper clinical setting in most cases. Although the frequency of such proarrhythmic events does not appear greater with Cordarone than with other agents used in this population, the effects are prolonged when they occur.

Even in patients at high risk of arrhythmic death, in whom the toxicity of Cordarone is an acceptable risk, Cordarone poses major management problems that could be lifethreatening in a population at risk of sudden death, so that every effort should be made to utilize alternative agents first.

The difficulty of using Cordarone effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of Cordarone is given, and a response generally requires at least one week, usually two or more. Because absorption and elimination are variable, maintenance-dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 192 patients with ventricular tachyarrhythmias, 84 required dose reduction and 39 required at least temporary discontinuation because of adverse effects, and several series have reported 15 to 20% overall frequencies of discontinuation due to adverse reactions. The time at which a previously controlled life-threatening arrhythmia will recur after discontinuation or dose adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalization. Attempts to substitute other antiarrhythmic agents when Cordarone must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when Cordarone is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

PULMONARY TOXICITY: Cordarone may cause a syndrome of cough and progressive dyspnea with functional, radiographic, gallium, and pathological data consistent with pulmonary toxicity. Frequency usually varies from 2-7%, but can be as high as 10-17%. Thus, at start of therapy, perform baseline chest x-ray and pulmonary-function tests, including diffusion capacity. Repeat history, physical exam (PE), and chest x-ray every 3-6 months.

Promptly discontinue drug if patient develops cough or dyspnea. Usually, however, progress is slower if pulmonary toxicity develops.

Cordarone-induced pulmonary toxicity seems to result from impaired (hypersensitivity pneumonitis) or direct (interstitial/alveolar) pneumonitis) toxicity.

Hypersensitivity pneumonitis usually appears early in therapy; rechallenge results in a more rapid and severe recurrence. Bronchoalveolar lavage is procedure of choice to confirm diagnosis, made when ≥ 7 suppressor lymphocytes (CD8+ positive) lymphocytosis noted. Treat with steroids and stop Cordarone.

Interstitial/alveolar pneumonitis, characterized by diffuse alveolar damage, interstitial pneumonitis or lobular or lung fibrosis. Phospholipidosis (foamy cells, foamy macrophages) is present in most cases of Cordarone-induced pulmonary toxicity, however, this also occurs in approximately 50% of all Cordarone patients. Use these cells as therapy markers, not evidence of toxicity. If interstitial/alveolar pneumonitis is diagnosed, reduce dose or, preferably, withdraw Cordarone, especially if other acceptable antiarrhythmics are available. Where these measures were instituted, symptoms usually decreased in the next week, most clinical improvement was in first 2-3 weeks. Chest x-ray changes usually resolve in 2-4 months. Some experts feel steroids may be helpful. Prednisone (40-80 mg/day or equivalent dose) of other steroids have been used and tapered over several weeks. At times rechallenge at a lower dose will not result in return of toxicity. Reports suggest lower loading and maintenance doses are associated with a lower incidence of pulmonary toxicity.

In Cordarone patients, any new respiratory symptoms suggest a pressing, and pulmonary-function tests (with diffusion capacity). A 15% decrease in diffusion capacity has a high sensitivity but only a moderate specificity for pulmonary toxicity, as decreases in diffusion capacity approach 30%. Sensitivity increases but specificity decreases. A Gallium scan may also be performed.

Fatalities from pulmonary toxicity occur in about 10% of cases. However, when life-threatening arrhythmias exist, stop Cordarone (amiodarone HCl) cautiously if drug-induced pulmonary toxicity is suspected. As the most common cause of death in these patients is sudden cardiac death, first rule out other causes of respiratory impairment. Bronchoalveolar lavage or lung biopsy may be necessary to confirm the diagnosis, especially when there is no acceptable alternative therapy.

If hypersensitivity pneumonitis is diagnosed, stop Cordarone and treat with steroids. If Cordarone-induced interstitial/alveolar pneumonitis is diagnosed, stop Cordarone and, preferably, stop Cordarone or, minimally, reduce the dose. Some cases may resolve after dose reduction and steroid use. Sometimes, rechallenge at lower doses did not result in return of interstitial/alveolar pneumonitis; however, pulmonary lesions are irreversible in some.

WORSENED ARRHYTHMIA: Cordarone may cause serious exacerbation of a presenting arrhythmia, possibly enhanced by concomitant antiarrhythmic therapy. Exacerbation (about 2-5% in most series) includes new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion and Torsade de Pointes. Cordarone has caused symptomatic bradycardia or sinus arrest with suppression of escape foci in 2-4% of patients.

LIVER INJURY: Increased hepatic enzymes, usually asymptomatic, are seen frequently. Consider discontinuation or dose reduction if increase exceeds 3 times normal, or doubles in patient with elevated baseline. Rarely, hepatic failure has been fatal.

PREGNANCY - PREGNANCY CATEGORY D. Cordarone is embryotoxic (increased fetal resorptions and growth retardation) in rats at 18 times the maximum recommended oral maintenance dose. Similar results are seen in one mouse strain at about 1/2 the maximum recommended maintenance dose or higher, but not in a second strain nor in rabbits at doses up to 9 times the maximum recommended maintenance dose.

Neonatal hypo- or hyperthyroidism: In utero exposure can cause fetal harm. Thus, there are some reports of congenital goiter, hypothyroidism and hyperthyroidism. If used anytime during pregnancy, inform patient of potential fetal hazard. In general, use during pregnancy only if potential benefit to the mother justifies unknown fetal risk.

Precautions:

CORNEAL MICRODEPOSITS; IMPAIRMENT OF VISION: Corneal microdeposits appear in a majority of adults on Cordarone. Usually discovered only by slit-lamp, up to 10% of patients have symptoms like visual halos or blurred vision. Microdeposits are reversible if dose reduced or treatment stopped, if asymptomatic, no need to reduce dose or stop drug.

PHOTOSENSITIVITY: Seen in about 10% of patients, sun-barrier creams or protective clothing may afford some protection. On long-term therapy, may have a blue-gray skin discoloration of exposed skin. If complicating or excessive, consider withdrawal or dose reduction.

THYROID ABNORMALITIES: Cordarone inhibits conversion of thyroxine (T_4) to triiodothyronine (T_3) and may cause euthyroid hypothyroidism, decreased T_3, and increased levels of inactive reverse T_3 (rT_3) in clinically euthyroid patients. Due to its release of inorganic iodine, or perhaps other reasons, Cordarone can cause either hypo- or hyperthyroidism. Monitor thyroid function before treatment and periodically thereafter, particularly in the elderly and those with history of thyroid nodules, goiter, or other thyroid dysfunction. Due to slow elimination of Cordarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid-function tests may persist for weeks or months after withdrawal.

Hypothyroidism occurred in 2-4% of patients in most series, but in 8-16% in some. To treat, reduce Cordarone dose and/or give thyroid hormone supplement. Individualize therapy, may need to stop Cordarone.

Hyperthyroidism occurs in about 2% of patients; incidence may be higher with prior inadequate dietary iodine intake. Cordarone-induced hyperthyroidism is usually a greater hazard than hypothyroidism due to possible arrhythmia bases/heart failure aggravation. IF VERY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED. Flat TSH response to TRH is confirmatory. Since arrhythmia breakthrough may accompany Cordarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or Cordarone withdrawal. Antithyroid drugs, β-blockers (consider temporary steroid therapy may be needed. See full prescribing information for additional information regarding treatment).

SURGERY: *Hypotension Postbypass*: Rarely, hypotension as seen on cessation of cardiopulmonary bypass during open-heart surgery in Cordarone patients; relationship to Cordarone is unknown.

Adult Respiratory Distress Syndrome (ARDS): Rarely, ARDS occurs in Cordarone patients after surgery. Patients usually respond to vigorous respiratory therapy, but outcome is fatal at times. Pathogenesis may be generation of superoxide radicals during oxygenation; therefore, keep operative F_iO_2 as close to room air as possible.

LABORATORY TESTS: Elevated liver enzymes (SGPT and SGOT) can occur; monitor closely if high maintenance doses used. Consider dose reduction or stopping therapy if significant elevations persist or hyperbilirubinemia occurs.

Thyroid-function tests (increased T_4 and reverse T_3, and decreased T_3) may be altered; despite these changes, most patients remain clinically euthyroid.

DRUG INTERACTIONS: Few drug-drug interactions have been explored formally but most have shown an interaction. Thus, anticipate other interactions, especially drugs with potentially serious toxicity, like other antiarrhythmics. With its long, variable half-life, potential for interaction also exists with drugs given after stopping Cordarone.

Digitalis: Serum digoxin increases (by up to 70%) and may reach toxic levels; onset is about 1 day. **On initiation of Cordarone, review need for digitalis and reduce its dose by about 50% or stop it.** If digitalis continued, monitor serum levels closely and observe for toxicity. Precautions probably also apply to digitoxin.

Anticoagulants: Potentiation of warfarin-type prothrombin response is almost always seen and can result in serious or fatal bleeding. Prothrombin time may increase by 100%, onset is 3 to 4 days. **Reduce anticoagulant dose by 1/3 to 1/2, and monitor prothrombin times closely.**

Antiarrhythmic Agents: Although they have been used concurrently with Cordarone, steady-state levels of quinidine, procainamide, and phenytoin may increase during such combined therapy. Quinidine serum concentrations may increase by 33% within 2 days. Procainamide serum concentrations may increase by 55%

such combinations for patients with life-threatening ventricular arrhythmias incompletely responsive to a single agent, or incompletely responsive to Cordarone (amiodarone HCl), and start any added antiarrhythmic at a lower than usual dose with careful monitoring. During transfer to Cordarone, reduce dose of previous agents 30-50% several days after adding Cordarone, when arrhythmia suppression should be startling. After Cordarone effects are established, discontinue other antiarrhythmics if possible. If treatment is maintained, continue monitoring carefully for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias. In Cordarone patients requiring additional antiarrhythmic therapy, initial dose of such agents should be approximately 1/2 of the usual dose.

Use Cordarone cautiously with β-blockers or calcium antagonists as bradycardia, sinus arrest, and AV block may be potentiated; if necessary, Cordarone can continue after pacemaker insertion in patients with severe bradycardia or sinus arrest.

ELECTROLYTE DISTURBANCES: May be ineffective or arrhythmogenic if hypokalemia is present; correct any potassium or magnesium deficiency before starting drug.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Fertility reduced in male and female rats at 8 x the highest recommended human maintenance dose. Cordarone caused a statistically significant, dose-related increase in thyroid tumors in rats. Incidence greater than control even at lowest dose tested, i.e., about 1/2 the T_3 -sparing recommended human maintenance dose. Mutagenicity studies were negative.

PREGNANCY: PREGNANCY CATEGORY D — See **Warnings.**

LABOR AND DELIVERY: Occurrence of adverse effects during labor or delivery is unknown. Preclinical studies in rodents have shown no effect on gestation duration or parturition.

NURSING MOTHERS: Cordarone is excreted in human milk; breastfeeding may expose nursing infants to a significant drug dose. Nursing offspring of lactating rats given Cordarone were less viable and had reduced body-weight gains. Advise mothers to discontinue nursing before taking.

PEDIATRIC USE: Safety and effectiveness have not been established.

Adverse Reactions: Adverse effects are very common (about 3/4 of all patients) with doses of 600 mg/day or more, and cause 7-18% to discontinue. The most serious are pulmonary toxicity, arrhythmia exacerbation, and rare serious liver injury (see **"Warnings"**), but other adverse effects constitute major management problems. These are often reversible by reducing dose and virtually always reversible by stopping Cordarone. Most adverse effects appear more frequent with continued treatment beyond 6 months; most appear relatively less frequent beyond one year. Neurologic problems, including malaise and fatigue, tremor and involuntary movements, poor coordination and gait, and peripheral neuropathy are common (20-40% of patients); these may respond to dose reduction, rarely need to stop therapy.

Gastrointestinal (GI) complaints, commonly seen with high doses (i.e., loading dose), usually respond to dose reduction or divided doses; rarely need to stop drug.

Asymptomatic corneal microdeposits. See **Precautions** and full prescribing information.

Photosensitivity. See **Precautions** and full prescribing information.

Cardiovascular adverse reactions, other than arrhythmia exacerbation, include the uncommon occurrence of congestive heart failure (3%) and bradycardia. Bradycardia usually responds to dose reduction but may require a pacemaker. CHF rarely requires stopping drug. Cases of conduction abnormalities occur infrequently and are reversible upon stopping drug.

The following side-effect rates are based on a retrospective study of 241 patients treated for 2 to 1,515 days (mean 441.3 days).

Each reported in 18-33% of patients: GI–Nausea and vomiting.

Each reported in 4-9% of patients: Dermatologic–Solar dermatitis/photosensitivity; Neurologic–Malaise and fatigue, tremor/abnormal involuntary movements, loss of coordination, abnormal gait/ataxia, dizziness, paresthesias; GI–Constipation, anorexia; Opthalmologic–Visual disturbances, Hepatic–Abnormal liver-function tests; Respiratory–Pulmonary inflammation or fibrosis.

Each reported in 1-3% of patients: Thyroid–Hypo- or hyperthyroidism; Neurologic–Decreased libido, insomnia, headache, sleep disturbances; Cardiovascular–CHF, cardiac arrhythmias, 3A node dysfunction, GI–Abdominal pain; Hepatic–Nonspecific hepatic disorders; Other–Flushing, abnormal taste and smell, edema, abnormal salivation, coagulation abnormalities.

Each reported in < 1% of patients: Blue skin discoloration, rash, spontaneous ecchymosis, **alopecia**, hypotension, and cardiac conduction abnormalities. Rarely hepatitis, cholestatic hepatitis, cirrhosis, optic neuritis, epididymitis, vasculitis, pseudotumor cerebri, and thrombocytopenia.

Adverse reactions most frequently requiring Cordarone discontinuation include pulmonary infiltrates or fibrosis, paroxysmal ventricular tachycardia, CHF, and elevated liver enzymes. Symptoms causing discontinuation less often include corneal disturbances, solar dermatitis, blue skin discoloration, hyper- or hypothyroidism.

Overdosage: The few reports of Cordarone overdose, in which 3 to 8 grams were taken, resulted in no deaths or permanent sequelae. Animal studies indicate that Cordarone has a high oral LD_{50} (>2,000 mg/kg).

Along with general supportive measures, monitor pet ent's cardiac rhythm and blood pressure. If bradycardia ensues, may use a β-adrenergic agonist or pacemaker. Use positive inotropic and/or vasopressor agents to treat hypotension with inadequate tissue perfusion. Neither Cordarone nor its metabolite is dialyzable.

Dosage and Administration: See full prescribing information.

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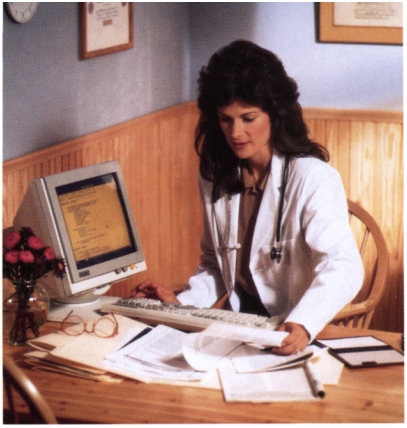
Manufactured for:
Wyeth-Laboratories Inc., Philadelphia, PA 19101
by **Sanofi, S.A.**, Paris, France, by arrangement with
Sanofi Pharmaceuticals, Inc.

WYETH-AYERST LABORATORIES
Philadelphia, PA 19101



ARMING YOURSELF WITH THE DATA

Access the current literature linking oxidants to disease. The growing body of clinical data provides insight into the effects of oxidants—free radicals and singlet oxygen, among others—in living systems. Oxidants can injure cells—even kill them. They can peroxidize unsaturated fatty acids,[1-4] inactivate enzymes[1] and cause mutations by damaging DNA.[1,5]

These dangerous, highly reactive molecules are generated endogenously as by-products of normal and pathological metabolism[1,6] and through exposure to ionizing radiation,[7,8] sunlight[8] and certain drugs.[7] But they can also enter the body from sources such as air pollution and cigarette smoke.[6,7]

Free radicals have been implicated in the pathogenesis of cataracts,[9-11] cancer,[1,5] emphysema,[8] ischemia-reperfusion injury,[12,13] Parkinson's disease,[14] rheumatoid arthritis[8] and in the aging process itself.[8,15] Lipid peroxidation has been associated with atherosclerosis[4,16,17] and damage to plasma and organelle membranes.[2,3]

Ordinarily, the body defends itself against free radicals and other oxidants and minimizes their damage by neutralizing them with enzymes (superoxide dismutase, catalase, peroxidases), scavengers of free radicals such as glutathione, and antioxidant nutrients—beta carotene and vitamins C and E.[7,18,19] While there is little we can do to alter the body's production of protective enzymes, we can enhance our defense systems by assuring adequate intakes of vitamins C, E and beta carotene.

Beta carotene potently quenches singlet oxygen[1] and other oxidants[3] even where oxygen tension is low,[18] such as at the organelle level. Vitamin C neutralizes free radicals, including the superoxide radical, and singlet oxygen[7]; and vitamin E can break the self-propagating peroxidative chain reaction of lipids.[1-3]

ARMING EVERYONE WITH THE RIGHT NUTRIENTS

Now, more than ever, people are concerned about their health and how to preserve it. Many people have already changed their eating habits accordingly, stressing low-sodium, low-fat and high-fiber foods. But how many of your patients know about oxidation and disease? Or how many are eating fruits and vegetables rich in antioxidant vitamins? Based on NHANES II data, it has been estimated that on any given day, 91% of the American population does not meet the USDA/DHHS fruit and vegetable guidelines (2+ fruits and 3+ vegetables). Eleven percent had no fruit or vegetables at all, 45% had no fruit, while 22% had no vegetable servings.[20]

Now, you can do more than ever to help. Your advice on diet and intake of antioxidant nutrients is important. A good place to start may be the healthy diets endorsed by the U.S. Department of Agriculture and the National Cancer Institute. For example, these diets designed to reduce the risk of cancer and other diseases provide about 5.2 to 6.0 mg of beta carotene each day. Americans typically consume only about 1.5 mg daily—leaving a substantial carotene gap.[21]

SUPPLEMENTS PROVIDE A POTENTIAL SAFEGUARD

For patients who continue to have antioxidant vitamin gaps because of special needs or resistance to changes in eating habits, consideration should be given to a dietary supplement. This will at least assure adequate intakes of vitamins C, E and beta carotene. Meanwhile, early indications from continuing studies on the role of antioxidant vitamins in lowering the risk of various chronic diseases offer considerable promise.

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ANTIOXIDANT PROTECTION VITAMIN C, VITAMIN E BETA CAROTENE

HHN 0412

rate ($r = 0.95$, $p > 0.00001$), but there was a tendency toward overestimation of the regurgitant flow rate by the mean accelerating flow rate when mitral regurgitation was more severe. Similar results were found for the stroke regurgitant volume. Thus, severity of mitral regurgitation of various causes can be quantitatively evaluated in patients by using the proximal accelerating flow calculation.

384 Determinants of Stroke Volume Response to Exercise in Patients With Mitral Stenosis: A Doppler Echocardiographic Study

MICHEL DAHAN, CATHERINE PAILLOLE, DENISE MARTIN, RENÉ GOURGON

The response of stroke volume to exercise was assessed with Doppler echocardiography at rest and during submaximal exercise in 27 patients with mitral stenosis and in 10 healthy control subjects. Stroke volume increased significantly during exercise in the control subjects but did not change significantly in the 27 patients, although it increased by ≥14% in 17 patients (Group I), remaining unchanged in the other 10 (Group II). Mitral velocity–time integral did not change in any group whereas calculated mitral valve area increased significantly in control subjects and patients in Group I, remaining unchanged in patients in Group II. The exercise change in calculated mitral valve area correlated significantly with both measured mitral valve area at rest and total mitral score. However, at constant mitral score, exercise change in calculated mitral valve area no longer correlated significantly with mitral valve area at rest. Therefore, in mitral stenosis, the exercise change in stroke volume depends on the change in mitral valve area, which is determined by the degree of mitral valve damage.

390 Percutaneous Balloon Mitral Valvotomy With the Inoue Single-Balloon Catheter: Commissural Morphology as a Determinant of Outcome

DIANE FATKIN, PAUL ROY, JOHN J. MORGAN, MICHAEL P. FENELEY

The importance to outcome and the predictability of commissural splitting by percutaneous balloon mitral valvotomy with the Inoue single-balloon catheter were examined in 30 consecutive patients. Commissural splitting occurred in 80% of patients, with a significantly greater mean increase in mitral valve area (85%) than if neither commissure split (13%). In contrast, there was no significant difference between the increase in mitral valve area in those patients with a total mitral echocardiographic score <8 and those with a score ≥8. The likelihood of commissural splitting was predicted from echocardiographic assessment of commissural morphology with 93% accuracy. Because commissural splitting is the major mechanism of successful balloon valvotomy, commissural morphology is a better predictor of outcome than is the total echocardiographic score.

398 Echocardiographic Description of the CarboMedics Bileaflet Prosthetic Heart Valve

JOHN CHAMBERS, JUSTIN CROSS, PHILLIP DEVERALL, EDGAR SOWTON

Few hemodynamic data about the CarboMedics prosthesis have been published despite its widespread use. Echocardiography was performed in 147 patients with a total of 96 normally functioning CarboMedics prostheses in the aortic position and 75 in the mitral position. The prosthesis offered relatively little resistance to forward flow except at small anulus diameters. These were a total of four washing leaks, one on either side of each pivotal point, and these lasted throughout systole or diastole. One jet was commonly more prominent than the other three and would be easy to misdiagnose as a sign of paraprosthetic regurgitation.

Pulmonary Hypertension

406 Pulmonary Artery Hemodynamics in Primary Pulmonary Hypertension

WARREN K. LASKEY, VICTOR A. FERRARI, HAROLD I. PALEVSKY, WILLIAM G. KUSSMAUL

Steady and pulsatile pulmonary artery hemodynamic variables were measured under rest conditions and during supine exercise in 8 patients with primary pulmonary hypertension and in 10 control subjects without detectable cardiovascular disease. Measures of pulmonary artery impedance and pulse wave transmission and reflection were substantially altered both at rest and during exercise in those with primary pulmonary hypertension. Moreover, elevations in both steady (resistive) and pulsatile (reflective) components of the vascular hydraulic load importantly influenced the abnormal exercise response in these patients.

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FLEXIPAK makes it simple to purge air from the flexible container before hanging to help reduce the potential for air emboli. The easily spiked port eliminates the possibility of infusing microscopic rubber particles from glass-bottle stoppers. And you don't need an air vent because the soft sides collapse as OMNIPAQUE flows.

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FLEXIPAK is flat and stackable for the best possible utilization of your storage space. And FLEXIPAK is available in the concentrations and sizes used most often.

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OMNIPAQUE 240	X	X	X
OMNIPAQUE 300	X	X	
OMNIPAQUE 350	X	X	X

It's all part of the package!

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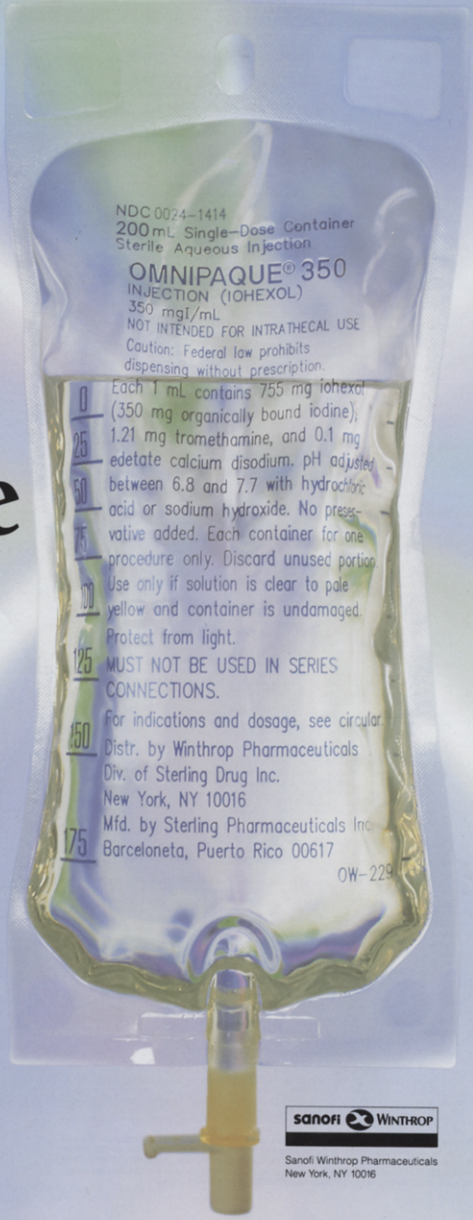

See last page for important product information concerning contraindications, warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations.

All nonionic iodinated contrast media currently available inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary to minimize thromboembolic events.

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New York, NY 10016

OMNIPAQUE® 140 | 240 | 300 | 350

INJECTION (IOHEXOL)
INTRAVASCULAR

PLEASE CONSULT FULL PRODUCT INFORMATION BEFORE USING. A SUMMARY FOLLOWS:

DESCRIPTION: OMNIPAQUE is a sterile, pyrogen-free and preservative-free, nonionic, water-soluble radiographic contrast medium for intravascular administration in concentrations of 140, 240, 300, and 350 mg/mL. OMNIPAQUE 140 contains 302 mg of iohexol equivalent to 140 mg of organic iodine per mL; OMNIPAQUE 240 contains 518 mg of iohexol equivalent to 240 mg of organic iodine per mL; OMNIPAQUE 300 contains 647 mg of iohexol equivalent to 300 mg of organic iodine per mL; and OMNIPAQUE 350 contains 755 mg of iohexol equivalent to 350 mg of organic iodine per mL. Each milliliter of iohexol solution contains 1.21 mg tromethamine and 0.1 mg edetate calcium disodium with the pH adjusted between 6.8 and 7.7 with hydrochloric acid or sodium hydroxide. Unused portions must be discarded. Iohexol solution is sensitive to light and should be protected from exposure.

CONTRAINDICATIONS: OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol.

WARNINGS — General: Nonionic iodinated contrast media inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications, may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

OMNIPAQUE should be used with extreme care in patients with: • any functional disturbances of the liver and kidneys, severe thyrotoxicosis, or myelomatosis. Diabetics with a serum creatinine level above 3 mg/dL should not be examined unless the possible benefits of the examination clearly outweigh the additional risk. OMNIPAQUE is not recommended for use in patients with anuria.

Radiopaque contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with the apparently resistant anuria. Although nephrectomy the contrast agent nor dehydration has separately proven to be the cause of anuria in myeloma, it has been speculated that the combination of both may be causative factors. The risk in myelomatous patients is not a contraindication; however, special precautions are necessary. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect. Myeloma, which occurs most commonly in persons over age 40, should be considered before instituting intravascular administration of contrast agents.

Ionic contrast media, when injected intravenously or intra-arterially, may promote sickling in individuals who are homozygous for sickle cell disease.

Administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The patient's blood pressure should be assessed throughout the procedure and measures for the treatment of hypertensive crisis should be readily available.

Reports of thyroid storm following the use of iodinated, ionic radiopaque contrast media in patients with hyperthyroidism or with an autonomously functioning thyroid nodule suggest that this additional risk be evaluated in such patients before use of any contrast medium.

Urography should be performed with caution in patients with severely impaired renal function and patients with combined renal and hepatic disease.

PRECAUTIONS — General: Diagnostic procedures which involve the use of radiopaque diagnostic agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for dealing with any complications of the procedure as well as for emergency treatment of severe reactions to the contrast agent itself. After parenteral administration of a radiopaque agent, competent personnel and emergency facilities should be available for at least 30 to 60 minutes, since severe delayed reactions have occurred (see ADVERSE REACTIONS: Intravascular — General).

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, in diabetic patients, and in susceptible nondiabetic patients (often elderly with preexisting renal insufficiency, intra- and small children. Dehydration in these patients seems to be enhanced by the osmotic diuretic action of urographic agents. It is believed that overnight fluid restriction prior to excretory urography generally does not provide better visualization in normal patients. *Patients should be well hydrated prior to and following administration of any contrast medium, excluding iohexol.*

Acute renal failure has been reported in diabetic patients with diabetic nephropathy and in susceptible nondiabetic patients (often elderly with preexisting renal disease) following excretory urography. Therefore, careful consideration of the potential risks should be given before performing this radiographic procedure in these patients.

Immediately following surgery, excretory urography should be used with caution in renal transplant recipients.

The possibility of a reaction, including syncope, life-threatening, fatal, cardiovascular reactions should always be considered (see ADVERSE REACTIONS: Intravascular — General). It is of utmost importance that a course of action be carefully planned in advance for immediate treatment of serious reactions, and that adequate and appropriate personnel be readily available in case of any reaction.

The possibility of an idiosyncratic reaction in susceptible patients should always be considered (see ADVERSE REACTIONS: Intravascular — General). The susceptible population includes, but is not limited to, patients with a history of a previous reaction to contrast media, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity to bronchial asthma, hay fever, and food allergies.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous for the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast medium, may be more accurate than pretesting in predicting potential adverse reactions.

A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised (see ADVERSE REACTIONS: Intravascular — General). Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered and administered using separate syringes. Recent administration of such premedication does not prevent serious, life-threatening reactions, but may reduce both their incidence and severity.

Even though the osmolality of OMNIPAQUE is low compared to diatrizoate- or iothalamate-based ionic agents of comparable iodine concentration, the potential transitory increase in the circulating blood volume in patients with congestive heart failure requires caution during injection. These patients should be observed for several hours following the procedure to detect delayed hemodynamic disturbances.

General anesthesia may be indicated in the performance of some procedures in selected adult patients; however, a higher incidence of adverse reactions has been reported in these patients and may be attributable to the inability of the patient to identify untoward symptoms, or to the hypotensive effect of anesthesia, which can reduce cardiac output and increase the duration of exposure to the contrast agent.

Angiography should be avoided whenever possible in patients with homocystinuria, because of the risk of inducing thrombosis and embolism.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be borne in mind during the catheter manipulations and contrast medium injection. Test injections to ensure proper catheter placement are recommended.

Selective coronary arteriography should be performed only in those patients in whom the expected benefits outweigh the potential risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing the procedure.

When OMNIPAQUE is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is present, do not use.

Information for Patients: Patients receiving injectable radiopaque diagnostic agents should be instructed to:

1. Inform your physician if you are pregnant.
2. Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homozygous sickle cell disease, or known thyroid disorder (see WARNINGS — General).
3. Inform your physician if you are allergic to any drugs, food, or if you had any reactions to previous injections of dyes used for x-ray procedures (see PRECAUTIONS — General).
4. Inform your physician about any other medications you are currently taking, including norepinephrine drugs, before you are administered this drug.

Drug/Laboratory Test Interaction: If iodine-containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine-binding capacity of thyroid tissue may be reduced for up to 2 weeks after contrast medium administration. Thyroid function tests which do not depend on iodine estimation, eg, T_3 resin uptake or direct thyroxine assays, are not affected. Many radiopaque contrast agents are incompatible in vitro with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenesis, or whether OMNIPAQUE can affect fertility in men or women.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits with up to 100 times the recommended human dose. No evidence of impaired fertility or harm to the fetus has been demonstrated due to OMNIPAQUE. There are, however, no studies in pregnant women because animal reproduction studies are not always predictive of human response; this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known to what extent iohexol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media is administered to nursing women. Bottle feedings may be substituted for breast feedings for 24 hours following administration of OMNIPAQUE.

Pediatric Use: Probably, patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine > 1.5 mg/dL, or those less than 12 months of age.

ADVERSE REACTIONS

Intravascular — General: Adverse reactions following the use of OMNIPAQUE are usually mild to moderate in severity. However, serious, life-threatening, and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media, including OMNIPAQUE. The injection of contrast media is frequently associated with the sensation of warmth and pain, especially in peripheral angiography, pain and warmth are less frequent and less severe with OMNIPAQUE than with many contrast media.

Cardiovascular System: Arrhythmias including PVCs and PACs (2%), angina/chest pain (1%) and hypotension (0.7%). Others including cardiac failure, asystole, bradycardia, tachycardia, and vasovagal reaction were reported with an individual incidence of 0.3% or less. In controlled clinical trials involving 1,485 patients, one fatality occurred. A cause and effect relationship between this death and iohexol has not been established.

Nervous System: Vertigo (including dizziness and lightheadedness) (0.5%), pain (3%), vision abnormalities (including blurred vision and photomania) (2%), headache (2%), and taste perversion (1%). Others including anxiety, fever, motor and speech dysfunction, convulsion, paresthesia, somnolence, stiff neck, hemiparesis, syncope, shivering, transient ischemic attack, cerebral infarction, and hypertonia were reported with an individual incidence of 0.3% or less.

Respiratory System: Dyspnea, rhinitis, coughing, and laryngitis, with an individual incidence of 0.2% or less.

Gastrointestinal System: Nausea (2%) and vomiting (0.7%). Others including diarrhea, dyspepsia, cramp, and dry mouth were reported, with an individual incidence of less than 0.1%.

Skin and Appendages: Urticaria (0.3%), purpura (0.1%), abscess (0.1%), and pruritus (0.1%).

Individual adverse reactions which occurred to a significantly greater extent for a specific procedure are listed under that indication in full prescribing information.

Pediatrics: In controlled clinical trials involving 391 patients for pediatric angiocardiography, urography, and contrast-enhanced computed tomographic head imaging, adverse reactions following the use of OMNIPAQUE 240, OMNIPAQUE 300 or OMNIPAQUE 350 were generally less frequent than with adults.

Cardiovascular System: Ventricular tachycardia (0.5%), 2:1 heart block (0.5%), hypertension (0.3%), and anemia (0.3%).

Nervous System: Pain (0.8%), fever (0.5%), taste abnormality (0.5%), and convulsion* (0.3%).

Respiratory System: Congestion (0.5%) and apnea (0.3%).

Gastrointestinal System: Nausea (1%), hypoglycemia (0.3%), and vomiting (2%).

Skin and Appendages: Rash (0.3%).

General Adverse Reactions to Contrast Media: Physicians should remain alert for the occurrence of adverse effects in addition to those discussed above. The following reactions have been reported after administration of other intravascular iodinated contrast media, and rarely with iohexol. *Reactions due to chemotoxic effects:* Hemolysis and erythrolysis. Hemodynamic reactions: vein cramp and thrombophlebitis following intravenous injection. Cardiovascular reactions: rare cases of cardiac arrhythmias, reflex tachycardia, chest pain, cyanosis, hypertension, hypotension, peripheral vasodilatation, shock, and cardiac arrest. *Renal reactions:* occasionally transient proteinuria, and rarely, oliguria or anuria. Allergic reactions: asthmatic attacks, nasal and conjunctival symptoms, dermal reactions such as urticaria with or without pruritus, as well as pharyngeal or laryngeal edema, and laceration, and rarely anaphylactoid reactions. More severe reactions have occurred due to this or unknown causes. *Signs and symptoms related to the respiratory system,* pulmonary or laryngeal edema, bronchospasm, dyspnea; or to *the nervous system* restlessness, tremors, convulsions. Other reactions: flushing, pain, warmth, metallic taste, nausea, vomiting, anxiety, headache, confusion, pallor, weakness, transient localized areas of edema (especially facial cramps), neutropenia, and dizziness. Rarely, immediate or delayed rigors can occur, sometimes accompanied by hyperpyrexia. Infrequently, "iodism" (salivary gland swelling) from organic iodinated compounds appears 2 days after exposure and subsides by the 5th day.

In general, the reactions which are known to occur upon parenteral administration of iodinated contrast agents are possible with any nonionic agent. Approximately 95% of adverse reactions accompanying the use of water-soluble intravascularly administered contrast agents are mild to moderate in degree. However, severe, life-threatening anaphylactoid reactions, mostly of cardiovascular origin, have occurred. Reported incidences of death range from 0.6 per 1 million (0.000064%) to 1 in 10,000 (0.01%). Most deaths occur during injection or 5 to 10 minutes later, the main feature being cardiac arrest, with cardiovascular disease as the main aggravating factor. Isolated reports of spontaneous confusion and shock are found in the literature. The incidence of shock is estimated to be 1 out of 20,000 (0.005%) patients.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast media, the dose, and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of dose injected, the speed of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that in the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Most adverse reactions to injectable contrast media appear within 1 to 3 minutes after the start of injection, but delayed reactions may occur.

Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with angiocardiography than with other procedures. Cardiac decompensation, serious arrhythmias, angina pectoris, or myocardial infarction may occur during angiocardiography and left ventriculography. Electrocardiographic and hemodynamic disturbances are less frequently with OMNIPAQUE than with Diatrizoate meglumine and diatrizoate sodium injection.

CONSULT PACKAGE INSERT FOR A MORE DETAILED DISCUSSION OF ADVERSE REACTIONS FOR INTRAVASCULAR USE OF OMNIPAQUE.

OVERDOSAGE: Overdosage may occur. The adverse effects of overdosage are life threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms include cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma, and cardiac arrest. Treatment of an overdosage is directed toward the support of all vital functions and prompt institution of symptomatic therapy.

The intravenous LD_{50} values of OMNIPAQUE (in grams of iodine per kilogram body weight) are 24.2 in mice and 15.0 in rats.

DOSAGE AND ADMINISTRATION: Details are provided in the package insert.

Sanofi Winthrop Pharmaceuticals
New York, NY 10016

OSW1 65-310470

identified at postoperative catheterization despite early repair; their presence may explain continuous murmurs or persistent cardiomegaly in patients with otherwise normal noninvasive findings. When clinically indicated, catheter-directed therapy can be performed with good results.

PHARMACOLOGY

471 **Effect of Zatebradine on Contractility, Relaxation and Coronary Blood Flow**

JEFFREY A. BREALL, JUN WATANABE, WILLIAM GROSSMAN

Zatebradine is similar in its structure to verapamil and is believed to act specifically at the sinoatrial node. We compared the effects of zatebradine and verapamil on heart rate, peak left ventricular pressure, its first derivative (dP/dt) and tau in isolated isovolumetric pig hearts. Zatebradine significantly decreased heart rate without affecting left ventricular pressure, dP/dt or tau. In contrast, verapamil markedly decreased peak left ventricular pressure and dP/dt and increased tau, with a lesser effect on heart rate. Subsequently, a continuous infusion of isoproterenol significantly increased heart rate, peak left ventricular pressure and dP/dt in the hearts treated with verapamil, whereas it only increased peak left ventricular pressure and dP/dt in the hearts treated with zatebradine, leaving heart rate unchanged. We also found that zatebradine had no effect on coronary blood flow in intact open chest pigs, whereas verapamil caused significant vasodilation. Zatebradine is a highly specific bradycardic agent whose effects are not overcome by beta-adrenergic stimulation. This agent may be useful in treating patients with angina or congestive heart failure.

EXPERIMENTAL STUDIES

478 **Doppler Color Flow Mapping of Epicardial Coronary Arteries: Initial Observations**

JAYASHRI R. ARAGAM, JOAN MAIN, J. LUIS GUERRERO, GUS J. VLAHAKES, JAMES F. SOUTHERN, MARK S. ADAMS, ARTHUR E. WEYMAN, ROBERT A. LEVINE

Echocardiographic imaging of the epicardial coronary arteries has been suggested as an adjunct to their intraoperative evaluation. Doppler color flow mapping could potentially enhance this evaluation by displaying flow disturbances produced by anatomic lesions of uncertain physiologic significance. This study addressed the hypothesis that coronary blood flow could be imaged and characteristic patterns described in normal and diseased vessels. Epicardial arteries were examined with a high resolution linear array transducer in the beating canine heart with and without experimental stenosis and in excised perfused canine hearts and human coronary arteries. Unlike normal segments, stenotic lesions exhibited localized aliasing, proximal acceleration, distal flow disturbance and recirculation. Lesions identified by these features in human arteries showed ≥50% lumen narrowing. Blood flow in the epicardial coronary arteries can therefore be imaged by Doppler color flow mapping and characteristic patterns described in normal and stenotic vessels.

488 **Exogenous Prostacyclin Decreases Vasoconstriction but Not Platelet Thrombus Deposition After Arterial Injury**

JULES Y. T. LAM, JAMES H. CHESEBRO, LINA BADIMON, VALENTIN FUSTER

The in vivo effects of increasing doses of prostacyclin (PGI_2) in vasoconstriction, platelet deposition and their interrelation were examined in an experimental porcine model of balloon arterial injury. There was a good correlation between injury-related vasoconstriction and platelet deposition in both control and PGI_2-treated pigs. However, this relation was such that for any given level of platelet deposition relative to control levels, PGI_2 decreased vasoconstriction in a dose-related manner. None of the three doses of PGI_2 administered (10, 50 or 500 ng/kg per min) decreased quantitative indium-111–labeled platelet deposition or the proportion of deeply injured arteries with mural thrombus compared with control values. Thus, intravenous infusion of PGI_2 significantly decreases vasoconstriction but not platelet deposition or mural thrombosis after arterial injury by balloon dilation. At hemodynamically tolerated doses, PGI_2 infusion probably will not prevent the thrombotic complications associated with angioplasty.

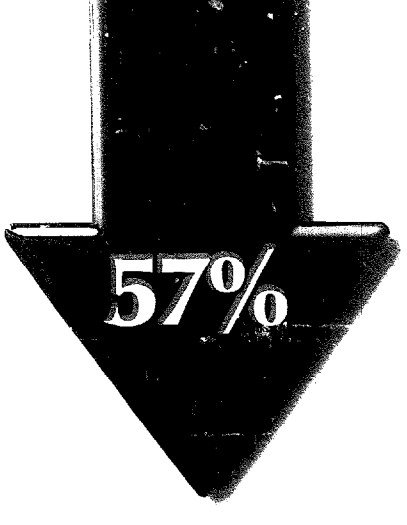
493 **Endogenous Prostaglandin Endoperoxides May Alter Infarct Size in the Presence of Thromboxane Synthase Inhibition: Studies in a Rabbit Model of Coronary Artery Occlusion–Reperfusion**

PAOLO GOLINO, GIUSEPPE AMBROSIO, BRUNO VILLARI, MASSIMO RAGNI, AMELIA FOCACCIO, LEONARDO PACE, FRED DE CLERK, MARIO CONDORELLI, MASSIMO CHIARIELLO

CHDetour:

LOPID reduced CHD* by 57% in triad patients†

In the Helsinki Heart Study, LOPID reduced heart attack by 57% in patients at very high risk and by 34% overall.‡ LOPID is indicated as adjunctive therapy to diet for reducing the risk of developing coronary heart disease **only** in type IIb patients without history of or symptoms of existing coronary heart disease who have had an inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid) known to reduce LDL cholesterol and raise HDL cholesterol **and** who have the following triad of lipid abnormalities: low HDL cholesterol in addition to elevated LDL cholesterol and elevated triglycerides.



In addition, the potential benefit of gemfibrozil in treating type IIa patients with elevations of LDL cholesterol only is not likely to outweigh the risks. LOPID is not indicated for the treatment of patients with low HDL as their only lipid abnormality.
LOPID is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil. LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis. Caution should be exercised when anticoagulants are given in conjunction with LOPID.

With baseline HDL above the median (46.4 mg/dL), the incidence of serious coronary events was similar for LOPID and placebo groups.
*Defined as a combination of definite coronary death and/or definite myocardial infarction. 57% calculated from an incidence of CHD of 149/1000 among placebo patients and 64/1000 among treated patients.
†Baseline LDL > 175 mg/dL, baseline TG > 200 mg/dL, and baseline HDL < 35 mg/dL.
‡All patients were counseled on dietary therapy and encouraged to exercise and quit smoking.

Please see adjacent page for brief summary of prescribing information.

PARKE-DAVIS BOOTS PHARMACEUTICALS

LOPID®
(gemfibrozil) 600-mg Tablets BID

TREATS THE TRIAD
REDUCES THE RISK OF DEVELOPING CHD

Lopid® (Gemfibrozil Tablets)

Before prescribing, please see full prescribing information. A Brief Summary follows.

CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.
2. Preexisting gallbladder disease (see WARNINGS).
3. Hypersensitivity to gemfibrozil.

WARNINGS

1. Because of differences in the histological and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of these studies, the Coronary Drug Project, 1103 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but there are many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 44%, higher rate of biliary tract mortality in the clofibrate-treated subjects as compared to placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in nonatherosclerotic liver disease, including fatal cirrhosis, and a 97% increase in gallbladder disease, including post-cholecystectomy complications, and pancreatitis. The majority of clofibrate deaths occurred during the open-label extension.

During the 5 year primary prevention component of the Helsinki Heart Study mortality rates are crude rates as of 2/84.

In the Lopid group and 43 (2.4%) in the placebo group, including the 2.5 year follow-up period since the trial was concluded, cumulative mortality from any cause was 106 (4.8%) in the Lopid group and 43 (4.9%) in the group assigned randomized to placebo (treated) ratio 1.20 in favor of placebo). Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality, from any cause between the Lopid and placebo groups at year 5 or at year 8.5 is not statistically significant. Even the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 5 year follow-up. However, many heart disease related mortality observed as in the group assigned randomized to Lopid at the two year follow-up (68 Lopid versus 45 placebo noncoronary deaths).

The incidence of cancer (excluding basal cell carcinoma) observed during the trial was at the 3.5 years after the trial was concluded was 31 (2.9%) in both originally randomized groups. In addition, there were 16 basal cell carcinomas in the group originally randomized to Lopid and 9 in the group originally randomized to the placebo ($p = 0.29$). There were 30 (1.4%) deaths attributed to cancer in the group originally randomized to Lopid and 18 (0.9%) in the group originally randomized to placebo ($p = 0.13$). Adverse outcomes, including carcinoma events, were higher in gemfibrozil patients. A corresponding study in men with a history of between six myocardial cases any heart disease to the secondary prevention component of the Helsinki Heart Study (see CLINICAL PHARMACOLOGY section) a halt prescribing intervention which includes the following: The secondary prevention component of the Helsinki Heart Study was conducted over 5 years in gas list and of the same centers in Finland in 628 middle-aged males excluded from the primary prevention component of the Helsinki Heart Study (excepting of a history of angina, myocardial infarction or unexplained ECG changes). The primary efficacy endpoint of the study was cardiac events. One death, of fatal and non-fatal myocardial infarctions and sudden cardiac deaths. The lowest rate (Lopid/placebo) for cardiac events was 1.47 (95% confidence limits 0.85, 2.45; $p=0.14$). Of the 25 patients in the Lopid group who experienced cardiac events, 12 patients suffered events, after discontinuation from the study. Of the 34 patients in the placebo group with cardiac events, 4 patients suffered events after discontinuation from the study. There were 17 C. disc deaths in the Lopid group and 8 in the placebo group (based ratio 2.14; 95% confidence limits 0.84, 5.05; $p=0.06$). Ten of these deaths in the Lopid group and 3 in the placebo group occurred after discontinuation from therapy. In this study of pr ients with known or suspected coronary heart disease, no benefit from Lopid treatment was observed in reducing cardiac ess , or cardiac deaths. Thus, Lopid has shown benefit only in selected dyslipidemic patients without suspected or established coronary heart disease. Men in patients with coronary heart disease and the lack of elevated LDL-cholesterol, elevated triglycerides, plus the HDL-cholesterol may possibly affect of Lopid on coronary events has not been adequately studied.

2. A gallstone prevalence substudy of 400 Helsinki Heart Study participants showed a trend toward a greater incidence of gallstones during the study with the Lopid treated group (25%) vs 15% for the placebo group, a 55% excess for the gemfibrozil group. A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (57 vs 11 subjects, 1 death events). The result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary heart disease has not been demonstrated and because liver and intermittent liver function tests were increased in rats, Lopid should be administered only to those patients (see and in the INDICATIONS AND USAGE section. If a significant serum lipid response is not observed, Lopid should be discontinued.

4. Concomitant Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Meticorol® (warfarin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinemia, leading in a large proportion of cases to acute renal failure. In VIRTUALLY ALL PATIENTS WHO HAVE HAD AN UNFAVORABLE OUTCOME, EITHER OR BOTH OF THESE POTENTIAL LIFE-THREATENING COMPLICATIONS OCCURRED. THERE IS NO EVIDENCE THAT CONCOMITANT LIPID THERAPY OF COMBINED THERAPY WITH LOVASTATIN AND/OR GEMFIBROZIL DOES NOT OUTWEIGH THE RISKS OF SEVERE MYOPATHY, RHABDOMYOLYSIS, AND ACUTE RENAL FAILURE (see Drug Interactions). The use of fibrates alone, including Lopid, rarely has occasionally been associated with myopathy. Patients receiving Lopid in concomitant oral anticoagulant therapy or treatment should have prompt medical evaluation for myalgia, muscle tenderness or muscle pain, weakness, or myositis a suspected or diagnosed Lopid therapy should be discontinued.

6. Cataracts: Subcapsular cortical cataracts occurred in 0% (3/4) of rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS

1. Laboratory Tests — Laboratory studies should be done to ascertain that the lipid levels are consistently observed. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. Combined Therapy — Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. Drug Interactions — (A) Bile Acid Sequestrant Interactions: Rhabdomyolysis has occurred with combined gemfibrozil and bile-acid therapy. It may be seen as early as 2 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with bile-acid sequestrant (other than cholestyramine and colestipol) should be weighed against the potential risk of myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) Sulfonylureas: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. Carcinogenesis, Mutagenesis, Impairment of Fertility — Long-term studies have been conducted in rats at 0.2 and 2 times the maximum dose (based on surface area, "equivalent"). The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant ($p = 0.1$). Male rats had a dose-related or a statistically significant increase of benign Leydig cell tumors. The higher dose females also had a significant increase in the combined incidence of benign and malignant lymphomas.

Long-term studies have been conducted in mice at 6 and 1 times the human dose (based on surface area). There were no statistically significant differences between controls in the incidences of liver tumors, but the doses tested were lower than those shown to be carcinogenic in other species.

Electron microscopic studies have demonstrated a fibrid necrotic myocardial degeneration following Lopid administration to the mice rat. An adequate study is lost for periodontal proliferation has not been done in humans but changes in periodontal morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class while liver biopsies were compared before and after treatment in the same individuals.

Administration of approximately 0.8 and 2 times the human dose (based on surface area) of Lopid to female rats — gemfibrozil during organogenesis caused a dose related decrease in fetal size as well as the high dose, an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia was noted.

Administration of 0.5 and 2 times the human dose (based on surface area) of Lopid to female rabbits during organogenesis caused a dose related decrease in fetal size as well as the high dose, an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia was noted.

5. Pregnancy Category C — It has been shown that gemfibrozil is embryotoxic in rats at doses 2 times the human dose (based on surface area) and fetal resorptions and suppression of pup growth during lactation.

Administration of 1 and 3 times the human dose (based on surface area) of Lopid to female rabbits during organogenesis caused a dose related decrease in fetal size as well as the high dose, an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia was noted.

There are no adequate and well-controlled studies in pregnant women. Lopid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects — Because of the similar dose-related embryotoxicity of Lopid to female rabbits during organogenesis caused a dose related decrease in fetal size as well as the high dose, an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia was noted.

6. Nursing Mothers — It is not known whether this drug is excreted in human milk, because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for Lopid in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

7. Hematological Changes — Mild normochromic, normocytic anemia, leukopenia, hemolytic anemia, thrombocytopenia, and white blood cell abnormalities have been observed on occasional patients following initiation of Lopid therapy. However, these events cannot during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. Liver Function — Abnormal liver function tests have been observed occasionally in some Lopid-treated patients. Therefore, periodic liver function studies are recommended and Lopid therapy should be discontinued if abnormalities persist.

9. Kidney Function — There have been records of worsening renal function in the addition of Lopid therapy in individuals with baseline plasma creatinine > 2.0 mg/dl. In such patients, the use of alternative therapy should be considered against the risks and benefits of a lower dose of Lopid.

10. Long-term Effectiveness — Safety and efficacy in children and adolescents have not been established.

ADVERSE REACTIONS

In the double-blind comparative clinical phase of the primary prevention component of the Helsinki Heart Study 3,046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects of the Lopid group:

	LOPID (N=2,046)	PLACEBO (N=2,030)
	Frequency in percent of subjects	
Gastrointestinal reactions	34.2	21.8
Dyspepsia	19.8	11.9
Abdominal pain	9.8	5.8
Acute appendicitis	1.2	0.6
(Pathologically confirmed in most cases where data were available)		
Renal dysfunction	0.7	0.1

Adverse events reported by less than 1% of subjects, but without a significant difference between groups:

Diarrhea	7.2	6.5
Fatigue	3.8	3.5
Nausea/Vomiting	2.3	1.9
Eczema	1.9	1.2
Rash	1.7	1.3
Vertigo	1.5	1.3
Constipation	1.4	1.3
Headache	1.2	1.1

Gastrointestinal surgery was performed at 6.0% of Lopid and 4.5% of placebo subjects in the primary prevention component a 4.4% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate component of the placebo group of the WHO study. Gallbladder surgery was performed almost more frequently in the Lopid group compared to placebo (1.9% vs. 0.9%; $p = 0.07$) in the secondary prevention component. A statistically significant increase in appendectomy in the gemfibrozil group was seen also in the secondary prevention component (8 on gemfibrozil vs. 0 on placebo, $p = 0.014$).

Nervous system and special senses adverse reactions were more common in the Lopid group. These included paresthesias, dizziness, and taste perversion. Other adverse reactions that were more frequent among Lopid-treated group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and pancreatitis.

From other studies it seems possible that Lopid is usually related to the occurrence of HEMOLOGIC/GALLSTN, SYMPTOMS (see WARNINGS), and to ABNORMAL LIVER FUNCTION TESTS and HEMMOLOGIC CHANGES (see PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil treated subjects than in other controlled clinical trials of 605 patients. Additional adverse reactions that have been reported on gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is possible or not established.

CAUSAL RELATIONSHIP POSSIBLE: Gastrointestinal: pancreatitis; jaundice; Central Nervous System: dizziness, somnolence, paresthesia, peripheral neuritis; decreased libido; aggression headache; eye blurred vision; Genitourinary: impotence; Musculoskeletal: myopathy, myasthenia, rhabdomyolysis; Hematological: anemia, leukopenia, eosinophilia; Hepatic: hepatomegaly; Miscellaneous: rash, urticaria, alopecia, photosensitivity, arthralgia, synovitis, vasculitis, pulmonary embolism; Clinical Laboratory: positive antinuclear antibody, hemoglobinuria, hematuria, albuminuria, hyperglycemia, glycosuria.

CAUSAL RELATIONSHIP NOT ESTABLISHED: Cancer: weight loss, Cardiac: arrhythmias, tachycardia, syncope, angina, myocardial infarction, cardiac failure, thromboembolism; Central Nervous System: depression, convulsions, syncope; eye: corneal edema, retinal hemorrhage, optic neuritis; Genitourinary: decreased libido, impotence, urinary frequency, urinary tract infection; Clinical Laboratory: positive antinuclear antibody, hemoglobinuria, hematuria, albuminuria, hyperglycemia, glycosuria; Miscellaneous: anaphylaxis, hemorrhage, anaphylaxis, Lupus-like syndrome, idiopathic intussusception, idiopathic interstitial pneumonitis.

DRUG/DRUG INTERACTIONS

The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

OVERDOSAGE

No information has been reported cases of overdosage, symptomatic supportive measures should be taken should it occur.

HOW SUPPLIED

Lopid (fibrozil 1.3) tablets, film-coated, scored tablets, each containing 600 mg gemfibrozil, are available as follows:

NDC 0071-0727-30 Bottles of 30

NDC 0071-0727-60 Bottles of 60

NDC 0071-0727-40 Unit dose packages of 100 (10 strips of 10 blisters each)

Store at 25°C (77°F).

Storage: Store below 30°C (86°F).

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Caution - Federal law prohibits dispensing without prescription.

(9/29/89)

Revised April 1992

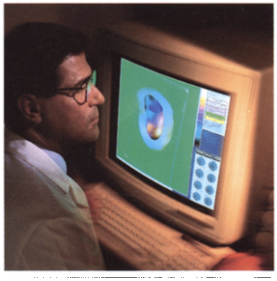
PARKE-DAVIS

Division of Warner-Lambert Company

This study assessed whether prostaglandin endoperoxides, which continue to be formed in the setting of thromboxane A_2 synthase inhibition, might influence the fate of ischemic myocardium in a model of coronary occlusion and reperfusion. The pure thromboxane/prostaglandin H_2 receptor antagonist, SQ 29548, did not significantly reduce infarct size compared with that in control animals, whereas dazoxiben, a selective thromboxane A_2 synthase inhibitor, significantly reduced infarct size at the end of the reperfusion period. In rabbits receiving R 68070, a new compound with simultaneous thromboxane A_2 synthase-inhibiting and receptor-blocking properties, infarct size was significantly smaller compared with dazoxiben-treated rabbits. This protective effect of R 68070 was completely abolished when the drug was administered with aspirin. Thus, prostaglandin endoperoxides play an important role in modulating the cardioprotective effects of thromboxane A_2 synthase inhibitors. The simultaneous inhibition of thromboxane A_2 synthase and blockade of thromboxane A_2/prostaglandin H_2 receptors by R 68070 identify a pharmacologic interaction of potential therapeutic importance.

Subject: Cardiac Imaging

Point of view: Cardiologist



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with magnetic resonance.

Myocardial perfusion

and contractility quantification studies.

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CARDURA is well tolerated. In placebo-controlled studies, only three common side effects were reported significantly more often than with placebo: dizziness, somnolence, and fatigue. These were generally mild and transient. Only 2% of patients discontinued therapy due to adverse effects— the same as with placebo. Syncope has been reported, but rarely (<1%).

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